A STUDY ON INTERSTITIAL LUNG DISEASE ASSOCIATED WITH RHEUMATOID ARTHRITIS

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CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON INTERSTITIAL LUNG DISEASE ASSOCIATED WITH RHEUMATOID ARTHRITIS**" submitted by **Dr. NIKHILA G.S** appearing for Part II M.D Branch I General Medicine Degree examination in April 2012is a bonafide record of work done by her under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to The Tamil Nadu Dr.M.G.R Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the Dissertation titled **"A STUDY ON INTERSTITIAL LUNG DISEASE ASSOCIATED WITH RHEUMATOID ARTHRITIS"** was done by me at Coimbatore Medical College & Hospital during the period from September 2010 to August 2011 under the guidance and supervision of **Prof. Dr. S. Veerakesari MD.** This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch I) in General Medicine.

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Dr. Nikhila G.S

ABBREVIATIONS

AAS – Atlanto axial subluxation

α1-AT – Alpha 1 antitrypsin

ACR – American college of rheumatology

BAL – Broncho alveolar lavage

BOOP – Bronchiolitis obliterans organizing pneumonia

CCP – Cyclic citrullinated peptide

CMV – Cytomegalo virus

COPD – Chronic obstructive pulmonary disease

CRP – C reactive protein

CTD – Connective tissue disease

CTD-ILD – Interstitial lung disease associated with connective tissue disease

DAD – Diffuse alveolar damage

DIP – Desquamative interstitial pneumonitis

D_LCO – Diffusion capacity of the lung for carbon monoxide

DMARDs – Disease modifying anti rheumatic drugs

DZ – Dizygotic

ESR – Erythrocyte sedimentation rate

FcRL3 – Fc receptor like 3

FEV1 – Forced expiratory volume in 1 second

FVC – Forced vital capacity

GGO – Ground glass opacity

HLA – Human leucocyte antigen

HP – Histopathology

HRCT – High resolution computed tomography

ILD – Interstitial lung disease

IPF – Idiopathic pulmonary fibrosis

LIP – Lymphocytic interstitial pneumonitis

MCP – Meta carpo phalangeal

MHC – Major histocompatibility complex

MTP – Metatarsophalangeal

MZ – Mono zygotic

NSIP – Non specific interstitial pneumonia

PADI4 – Peptidyl arginine deiminase type IV

PFT – Pulmonary function testing

PIP – Proximal inter phalangeal

PTPN22 – Protein tyrosine phosphatase non-receptor 22

RA – Rheumatoid arthritis

RF – Rheumatoid factor

RA-ILD – Interstitial lung disease associated with rheumatoid arthritis

SE – Shared epitope

SLE – Systemic lupus erythematosus

TNF-**α** – Tumour necrosis factor – alpha

UIP – Usual interstitial pneumonia

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ABSTRACT

Objective –To describe the clinical features, laboratory profile, radiographic patterns, pulmonary function tests abnormalities and broncho-alveolar lavage cytology of patients with RA-ILD, and to see if they correlate with each other.

Methods – Patients with the definite diagnosis of RA attending rheumatology clinic were screened clinically for pulmonary signs and symptoms of RA-ILD. All patients with clinical suspicion of ILD underwent chest imaging studies including X-ray and HRCT. Those with radiological evidence of ILD were included in the study and were subjected to pulmonary function test and broncho-alveolar lavage along with other blood investigation. Their clinical, radiological and spirometry characteristics were noted and analyzed.

Results – A total of 30 patients comprising 18 females and 12 males with mean age of 56.2 years were included. Mean duration of joint symptom was 7.03 years & pulmonary symptom was 3.16 years. The average duration of joint symptoms after which the pulmonary symptoms begin to manifest was 3.87 years. Dyspnoea was the most common presenting symptom (19 patients or 63.3%), followed by cough (11 patients or 36.6%). Bibasilar crackles were the most common pulmonary sign (28patients or 93.3%). 23 patients (76.7%) had positive RA factor. Reticular pattern was the predominant radiological finding in both X-ray (46.7%) and HRCT (53.3%). Nine patients (30%) with no evidence of ILD in X-ray had ILD findings in HRCT. Most patients (86.6%) showed restrictive abnormality in PFT. Neutrophilic alveolitis was seen in 5 out of ten patients who underwent BAL.

Conclusion - Interstitial lung disease associated with rheumatoid arthritis (RA-ILD) affects men and women in their late middle age, and can present within few years of occurrence of joint symptoms. HRCT is the most useful test in evaluating suspected patients of RA-ILD compared to X-ray. Pulmonary function test is a useful in assessment and follow up of these patients.

Key words – Rheumatoid arthritis, Interstitial lung disease, HRCT, Pulmonary function test

INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic disease that manifests as inflammatory arthritis of multiple joints and produces a wide variety of extra articular manifestations. It affects approximately 1% of adult population[1] worldwide and occurs more commonly in females than in males (2-3:1 ratio).[2]

Due to its systemic nature, RA may result in a variety of extra articular manifestations. Previous studies have shown that nearly 50% of patients with RA demonstrate some type of extra-articular manifestation involving skin, eye, heart and lungs.[3,4,29]

Lung disease is the second most common cause of death in RA[5,6]. Interstitial lung disease (ILD) is one of the important pulmonary manifestations of RA like other connective tissue diseases (CTDs). However, ILD associated with RA (RA-ILD) differs both histopathologically and prognostically from other connective tissue diseases associated ILD (CTD-ILD). Non specific interstitial pneumonia (NSIP) pattern predominates in most CTD-ILD whereas usual interstitial pneumonia (UIP) pattern is more common in RA and appears to predict worse survival.[7,8,9]

RA-ILD is associated with significant morbidity and mortality. It can lead to progressive fibrosis after variable duration and intensity of disease. The diagnostic workup of RA-ILD include chest imaging (X-ray and HRCT),

pulmonary function testing (PFT) including diffusion capacity of the lung for carbon monoxide (DL_{CO}) and lung biopsy. Bronchoalveolar lavage (BAL) and cellular analysis of fluid are useful in excluding the various other causes for interstitial pneumonitis.

The role of these investigations in the diagnostic work up of patients with RA-ILD and their correlation between each other and with histopathology is a subject of recent interest. There is very little data regarding the different HRCT patterns and its correlation with PFT abnormality in Indian population. Hence we decided to do this research work to find out the prevalence of X-ray abnormality, different HRCT patterns and their correlation with PFT in our setting. At present there is no clear consensus regarding the work up of RA patients for early detection of ILD, the investigation of choice in RA-ILD and its management options. We hope that this study could provide the baseline data from which future guidelines regarding the management of RA-ILD in Indian patients could evolve.

OBJECTIVES OF THE STUDY

The study is aimed at

1. Describing the clinical features, laboratory profile, radiological patterns, pulmonary function test (PFT) abnormalities and broncho-alveolar lavage (BAL) cytology of patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).
2. To see if these diagnostic and assessment tools correlate among each other and also with the clinical features of the patients.

REVIEW OF LITERATURE

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease. The main characteristic is a persistent synovitis of joints, often symmetrical in distribution, resulting in pain, stiffness, and loss of function. RA has a wide clinical spectrum varying from mild joint symptoms to severe inflammation and damage to joints. In addition, being a systemic rather than a localized disease, a wide variety of extra-articular features like rheumatoid nodules, vasculitis, lymphadenopathy, serositis, and amyloidosis may develop. Our study focuses on one such extra articular manifestation namely interstitial lung disease (ILD).

Historical review

Early descriptions of rheumatoid arthritis in the contemporary medical literature can be traced back to the eighteenth century. Alfred Baring Garrod (1859) first used the term "rheumatoid" arthritis.[10] In the early days of modern medicine, rheumatoid arthritis, like other diseases of unknown causes, was thought to result from foci of infection.[11,12]

Klemperer et al[13] (1942) first proposed that conditions like systemic lupus and systemic sclerosis might result from diffuse primary degeneration of collagen after considering the fibrinoid changes, thereby giving the name collagen vascular diseases to these conditions. Rheumatoid arthritis was then added to the group of collagen vascular diseases. Rheumatoid factor was

discovered by Waaler et al[14] in 1940s in the blood of patients with rheumatoid arthritis. It is the first immunological marker of rheumatoid disease to be recognized and served to distinguish it from other forms of inflammatory arthritis.

Epidemiology of Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting 0.5% to 1% of the general population worldwide. The prevalence of RA is nearly constant throughout the world barring some exceptions. It has a lower prevalence in some countries like China (0.3%), whereas certain ethnical population like pima Indians have a higher prevalence (5%).[15] Women are affected approximately three times (2-3:1) more often than men. The prevalence increases with age, and sex differences diminish in the older age group.

Etiology

Although the etiology of RA is unknown, many studies suggest that a blend of environmental and genetic factors is responsible; both are necessary, but are insufficient alone for full expression of the disease. Genetic factors explain the susceptibility for RA in at least 60% of cases.

Genetics

Studies conducted on twins have indicated that there is an increased risk of disease concordance among monozygotic (MZ) twins. The MZ concordance

rate for RA is four times greater than the dizygotic (DZ) twin concordance rate, indicating a heritability of 40–60%.[16,17]

In the past, genetic studies have focused primarily on the role of the major histocompatibility complex (MHC) locus in RA, namely HLADR4 and HLADR1. MHC genes are responsible for about one third of the genetic risk for development of RA. Several studies have indicated that these HLA alleles are more strongly associated with features of severe disease, such as rheumatoid factor positivity, erosions, and nodules.[18] In Indian population, HLA DR1 is important as a genetic risk factor rather than HLA DR4. The term **shared epitope (SE)** is used to denote the HLA–β1 alleles that convey increased susceptibility for RA. It has been noted that person who carries SE allele is at increased risk of production of anti-CCP antibodies and also a poor prognosis.

Recently studies have identified certain non MHC genes involved in the genetic predisposition of RA. Some of the promoter regions identified is **PTPN22**, **FcRL3**, **PADI4**, **CTLA4** and most of these are involved in complex immunological signaling pathways.

Environmental factors

A number of agents including Epstein Barr virus, parvovirus, proteus, cytomegalovirus (CMV), retroviruses, mycoplasma, and mycobacteria have been proposed as possible triggers for the development of RA, but there is no

conclusive evidence until now. Smoking has been identified as an independent risk factor in the development of RA.[19]

Pathophysiology

The pathophysiology of RA is not clearly understood. Triggers like infection can initiate an abnormal autoimmune inflammatory response in genetically predisposed. The imbalance among the inflammatory mediators results in eventual damage to cartilage and bone.[20] Synovial inflammation and subsequent cascade of reactions leads to proliferation of synovial macrophages, fibroblasts, and chondrocytes in the articular cartilage. The enzymes secreted by these cells degrade proteoglycans and collagen, causing synovial tissue destruction.[20] This inflammatory reaction is accompanied by angiogenesis in the synovium, causing irregular regrowth of the synovial tissue forming invasive pannus tissue. This stimulates osteoclasts, resulting in further inflammation, more cartilage destruction and the characteristic bony erosions. Inflammatory mediators along with interleukins, tumor necrosis factor a (TNFα), cytokines, and proteinases leads to the development of systemic symptoms and the extra-articular manifestations of RA.[20,21] It is postulated that "shared epitope," possibly derived from the disease-associated HLA-DR4/1 allele act as a self antigen and sensitise Tcells.[22] Later, these T cells could be activated by cross reactive antigens expressing the shared antigen leading to

inflammation. It is postulated that multiple infectious agents reactivate RA by potentially cross-reactive peptides.[22]

Diagnosis of rheumatoid arthritis

There is no gold standard investigation available for the diagnosis of rheumatoid arthritis. The diagnosis is based on an effective clinical history, physical examination, laboratory tests, and exclusion of other diagnoses. In 1987, the American College of Rheumatology (ACR), in conjunction with the American Rheumatism Association, established 7 diagnostic criteria for clinical diagnosis of RA.[23]

When the disease is diagnosed within six months of onset of symptoms, it is termed as "Early RA. It has been demonstrated that early treatment has a positive impact on disease progression and prognosis. Hence there is considerable research being done on this subject.

Even at presentation, the treating physician should actively search for extra articular involvement as this will influence treatment options and determine the disease progression.

Criterion	Definition[#]
Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hr before maximal improvement
Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry
Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
Serum RF	Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in <5% of normal control subjects
Radiographic changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints
[#]for classification purposes, a patient shall be said to have RA if he or she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded	

Clinical features

Onset

A slow onset of RA over weeks to months is seen in 55% to 65% of cases.[24] An acute onset of symptoms that peak within a few days can occur in 8-15% of patients and an intermediate type of onset, in which symptoms develop over days or weeks, occurs in 15% to 20% of patients. The initial symptoms may be systemic or articular. The initial presentation can be nonspecific like fatigue, malaise, swollen hands, and diffuse musculoskeletal pain with joints becoming involved later. Morning stiffness is a cardinal sign that can appear even before pain.

Joint Involvement

The joints most commonly involved first in RA are the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, metatarsophalangeal joints, and wrists.[25] Larger joints generally are involved later. The distal interphalangeal and sacroiliac joints are usually not affected. Affected joints are usually warm, tender to palpation, and boggy. Symmetric joint swelling and tenderness on palpation is a characteristic feature of RA joint disease.

Progressive destruction of joints and soft tissues may lead to chronic irreversible deformities and functional impairment. Cervical spine involvement occurs in the form of atlanto-axial subluxation and can lead to compressive

myelopathy. Lumbar and thoracic spine is usually not involved. Temporomandibular joint can be involved, but functional impairment is rare.

Extra articular manifestations

RA is a systemic disease with a variety of extra articular manifestations. The exact prevalence and incidence of extra articular manifestations in RA is not known, but it is estimated that as many as 40% of patients may have extra articular manifestations, and in ~15% these are severe.

Extra articular manifestations may occur during the clinical course, even prior to the onset of arthritis. They are the major cause of mortality due to RA[26] with infection as the leading cause of death (25%), followed by cardiac and pulmonary disease (18%), with renal and gastrointestinal disease lower in frequency (10%).

Generally, extra articular manifestations occur in individuals with high titers of rheumatoid factor or with antibodies to CCP.

Some of the common extra articular manifestations are listed in the following table.

Extra articular manifestations of rheumatoid arthritis
Rheumatoid nodules of varying size and consistency are found in up to 25% of patients. ***Location*:** extensor area of the forearm (common), internal organs (rare). ***Complications***: gangrene and ulcer formation. **Hematologic**: normocytic, normochromic anemia; thrombocytosis or thrombocytopenia; lymphadenopathy. **Felty syndrome**: the association of RA with leukopenia and splenomegaly **Vasculitis**: may involve eyes, brain, skin, renal, cardiovascular, and gastrointestinal (GI) tract **Pulmonary**: pleural effusions, pulmonary nodules, interstitial lung disease, bronchiolitis obliterans with organizing pneumonia; complications of treatment with disease-modifying antirheumatic drugs (DMARDs) **Cardiac**: pericardial effusions; valvular lesions; cardiac manifestations from systemic influences of RA such as serositis, amyloidosis, vasculitis, conduction abnormalities secondary to nodule formation **Renal**: microalbuminuria (correlates with disease activity); mesangial glomerulonephritis; (nephritic syndrome); nephrotoxicity secondary to DMARDs **Ophthalmologic**: keratoconjunctivitis sicca or secondary Sjo'gren syndrome; episcleritis and scleritis (prompt treatment necessary to avert vision loss); effect of drug therapy—risk of retinopathy with hydroxychloroquine requires ongoing surveillance **Neurologic**: mononeuritis multiplex and central nervous system features including seizures, aseptic meningitis, and stroke secondary to vasculitis. Entrapment neuropathies via nerve impingement associated with subluxation of the atlantoaxial joint, amyloid deposits, or nodules **Musculoskeletal**: osteoporosis and fractures caused by disease process and corticosteroid treatment. Muscular weakness of varying etiology **Amyloidosis**: found in 21% of patients in postmortem studies of patients with RA
Data from Firestein GS, Panayi GS,Wollheim FA. Rheumatoid arthritis: frontiers in pathogenesis and treatment. New York: Oxford University Press; 2000.

Pulmonary involvement in RA

Lung is one of the extra articular organs to be affected in RA. In one reported series[37], lung disease is the second most common cause of death due to rheumatoid arthritis second only to cardiac disease.

In most of the cases joint symptoms of RA precede the onset of pulmonary symptoms. In few cases however, lung manifestations may precede the onset of joint symptoms, even by several years. This is particularly true for Non specific interstitial pneumonia (NSIP),[38,39] pleuritis, and occasionally obliterative bronchiolitis.

Pleuropulmonary complications are more likely to occur in patients with more severe chronic articular disease, with high titers of rheumatoid factor, and in patients who have subcutaneous nodules, as well as other systemic complications such as cutaneous vasculitis, myocarditis, pericarditis, ocular inflammation, and Felty's syndrome.

Many pulmonary manifestations are directly linked to RA itself and may be a result of underlying defects in immunity and chronic inflammation. Some are due to exposures and to the treatment of RA with disease-modifying antirheumatic drugs (DMARDs). Following is the table showing common pleuropulmonary manifestations in RA.

Table showing pulmonary manifestations of rheumatoid arthritis

Lung parenchyma
Interstitial lung disease (ILD) Usual interstitial pneumonitis (UIP) Nonspecific interstitial pneumonitis (NSIP) Bronchiolitis obliterans with organizing pneumonia (BOOP) Lymphocytic interstitial pneumonitis (LIP) Desquamative interstitial pneumonitis (DIP) Diffuse alveolar damage (DAD) Drug-induced pneumonitis Rheumatoid nodules (necrobiotic nodules) Caplan's syndrome (silicosis associated with RA) Infectious complications
Airways
Chronic obstructive pulmonary disease (COPD) Bullous emphysema Bronchiectasis Obliterative bronchiolitis (Constrictive bronchiolitis)
Pleura
Pleuritis Pleural effusion Spontaneous pneumothorax
Vascular
Pulmonary hypertension Diffuse alveolar hemorrhage Extrapulmonary Diaphragm weakness

Interstitial lung disease

The interstitial lung diseases are a diverse group of disorders characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium. ILD can occur either as a primary condition or secondary to multiorgan conditions such as connective tissue diseases (CTDs). It can be classified into two groups based on underlying histopathology.[27]

I) Those associated with predominant inflammation and fibrosis

Known cause – ex, drug induced, radiation, asbestosis

Unknown cause – idiopathic interstitial pneumonias, CTDs

II) Those associated with predominant granulomatous reaction

Known cause – organic or inorganic dust

Unknown cause – Sarcoidosis, Wegener's granulomatosis

Rheumatoid arthritis associated interstitial lung disease (RA-ILD)

Interstitial lung disease is one of the pulmonary manifestations of rheumatoid arthritis. The association between ILD and RA was first described by Ellman et al in 1948.[40]

There are notable differences between ILD occurring in other connective tissue disorders and ILD occurring in RA. It is one of the emerging fields of research in recent times.

Rajasekeran et al[55] has compared IPF with RA-ILD and has shown that RA-ILD has a better prognosis than IPF.

Epidemiology of RA-ILD

RA-ILD has a male preponderance of 3:1. ILD can occur in all CTDs whereas the highest prevalence is seen in systemic sclerosis. The lowest prevalence is seen in SLE. There is a wide variation in the reported prevalence of ILD in RA among various studies from 4% to 68% depending upon the diagnostic tool chosen for the study and the population selected for the study (asymptomatic, symptomatic) .[28,29,30,31]

The two major forms of ILD pattern in RA is Usual interstitial pneumonia (UIP) and Non specific interstitial pneumonia (NSIP). UIP carries a uniform bad prognosis whereas NSIP is treatable by anti inflammatory treatment. Idiopathic UIP is otherwise called as idiopathic pulmonary fibrosis (IPF).

Risk factors for ILD in RA

Smoking, male gender and long standing RA are reported as risk factors for development of ILD in RA.[32,33] Other risk factors proposed for pulmonary fibrosis were high titers of rheumatoid factor and the presence of rheumatoid nodules. Apart from this, genetic factors (human leukocyte antigen B40 and α1-antitrypsin) have been described.[34,35] Even though a recent study has proposed methotrexate therapy as a risk factor for disease progression, the numbers of

patients studied were small, and methods of detecting methotrexate toxicity were unclear in the study. The role of DMARDs in the pathogenesis or progression of ILD among RA patients is uncertain.

Pathogenesis of ILD

Pathogenesis of pulmonary fibrosis is initiated by microvascular injury, which leads to endothelial cell damage and alveolar epithelial injury. This leads to activation of the coagulation cascade, release of various cytokines and growth factors, and ultimately activation of fibroblasts, a key event in the development of fibrosis.

Clinical features of RA-ILD

It usually presents as insidious onset of exertional dyspnoea which is the commonest symptom. In some patients it may also be subclinical. The reason behind dyspnoea is exacerbation of hypoxemia and increased dead space ventilation in the early stages and high static recoil of the lung with increased work of breathing in the late stage. Most patients also have a non productive type of cough. A pleuritic type of chest pain can also occur.[41]

Pulmonary hypertension may develop after many years due to advanced pulmonary fibrosis leading to right ventricular strain and cor pulmonale. Physical examination may show clubbing and evidence of right heart failure in

advanced cases. Respiratory system examination shows bibasilar dry crackles in most patients with RA-ILD.

An acute presentation of the disease has been described[42] in patients with RA-ILD, particularly in patients with UIP pattern.[43,44] It is one of the dramatic manifestations of RA which takes the form of diffuse alveolar damage or acute interstitial pneumonia like picture. The corresponding HRCT finding is the presence of diffuse ground glass appearance with or without honeycombing.

Investigations

Laboratory tests

Blood investigations are useful in diagnosis and monitoring of RA in general. These investigations do not have a direct role in the evaluation of RA-ILD. But, as mentioned earlier, high RA titers are associated with severe extra articular manifestations.

Blood investigations include a complete blood cell count with differential count, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Renal and hepatic function parameters are also recommended mainly for monitoring drug reactions.

Rheumatoid factor (RF)

IgM isotype is the most frequently measured isotype in RA. Rheumatoid factor positivity is seen in 75-80 % of RA patients. Negative result does not exclude a diagnosis of RA.

Incidence of positivity increases with duration of disease and with age. Approximately 5% to 10% of healthy individuals are RF positive, and RF positivity is found in a number of other diseases also.

Anticyclic Citrullinated Peptide IgG Antibody (anti-CCP antibody)

Anti-CCP antibody is more specific for RA (95 % specificity). It is produced at the site of joint inflammation by the B cells, especially during the early part of the disease. It can be used in combination with RA factor with increased sensitivity. It has got prognostic value also with anti-CCP positivity is associated with more severe disease and worse prognosis.

Radiographic patterns

X-ray is not a sensitive tool to diagnose ILD in RA. The reported prevalence of ILD in RA based on chest x-ray was 1 to 5 %,[29] whereas HRCT is a highly sensitive diagnostic investigation for RA-ILD, and the reported prevalence of interstitial lung disease in early onset RA was 33%.[28, 46]

HRCT is the investigation of choice to identify and distinguish between UIP and NSIP and invasive investigations such as lung biopsy would be needed

only if HRCT is non diagnostic.[47, 48] There are four common radiographic patterns identified in patients with RA-ILD are,[45]

UIP-like pattern	Bilateral subpleural reticulation with or without honeycombing
NSIP-like pattern	Predominant ground-glass opacities
Inflammatory airway disease pattern	Centrilobular branching lines with or without bronchial dilatation
Organizing pneumonia-like pattern	Patchy areas of consolidation

Overall, **NSIP** is the most common type of interstitial lung disease pattern, whereas in rheumatoid arthritis, the most common ILD pattern is usual interstitial pneumonia **(UIP)**[36, 45] which carries a bad prognosis.

Pulmonary function tests in RA-ILD

The most common abnormality noted in PFT is restrictive defect with reduced FVC and normal or elevated FEV1/FVC ratio.

Diffusing lung capacity for carbon monoxide (DL_{CO})

In patients with RA-ILD, a reduced diffusing lung capacity for carbon monoxide (DL_{CO}) is often the earliest PFT abnormality[49] and DL_{CO} is the most sensitive test to diagnose the presence of ILD in RA although it is not specific for ILD. A reduced DL_{CO} can also occur if there is emphysema which can destroy the vascular beds. Dawson et al[44] found that 80% of patients with RA

had a reduced DLCO, while only 5–15% of patients had a purely restrictive defect on spirometry.

Broncho alveolar lavage (BAL)

BAL plays an important role as an investigatory tool to exclude some of the differential diagnoses of RA-ILD such as infections, drug reactions, malignancy and other co existing disease. 52% of patients with recent onset RA showed presence of alveolitis in BAL.[28] Patients with clinical interstitial pneumonia usually show neutrophilic alveolitis[52, 57] whereas approximately one third of patients with normal chest x-ray and PFTs revealed lymphocytic alveolitis.[56] Due to the fact that BAL is not useful in diagnosing RA-ILD it is not regularly included in the diagnostic work up of RA-ILD patients. It is done whenever there is a necessity to exclude infection or drug related ILD as a cause for interstitial pneumonia in RA patients. Bronchoscopy with BAL should be considered in the evaluation of new infiltrates in any RA patient receiving immunosuppressive therapy.

Histopathology in RA-ILD

Lung biopsy and histopathological examination is the gold standard investigation for diagnosis of RA-ILD. Among connective tissue disorders, the highest proportion of UIP is found in RA-ILD. Lee et al[36] found UIP as the

most common histopathologic pattern in RA-ILD patients (56%), followed by NSIP (33%) and organizing pneumonia (11%).

Correlation of histopathology and radiography in RA-ILD

Studies have demonstrated histopathologic pattern of IPF correlates with HRCT findings.[47, 50] Similarly, studies to demonstrate the correlation between histopathological pattern in RA-ILD and HRCT pattern are available. On the whole it has been observed that the presence of reticular shadows in HRCT correlates with the presence of UIP pattern in the lung biopsy specimen and the presence of ground glass pattern in the HRCT correlates with the presence of NSIP in the lung biopsy.[36, 45]

Association of pathophysiology to histopathological findings

Studies that looked into the difference in serological and lymphocyte profile between the two radiological patterns could not demonstrate a significant difference. Gochuico et al[51] demonstrated that patients BAL fluid of patients with UIP pattern in HRCT contained increased concentration of platelet derived growth factor AB, gamma-interferon and transforming growth factor-β. Lee et al[36] and Biederer et al[52] have showed that smoking habit was more prevalent among patients who showed UIP pattern in their HRCT.

Treatment of ILD in RA

There is no well controlled, randomized trial on the treatment of RA-ILD. Immunosuppressive therapy is the mainstay of treatment available for patients with progressive pulmonary disease. Supportive therapy with home oxygen and respiratory rehabilitation offers some help.

Lung transplantation is the final option available for those without significant involvement of other organ systems.

In asymptomatic patients with HRCT evidence of ILD, whether treatment offers substantial benefit is not yet clear. In symptomatic patients, studies have reported positive response to treatment with corticosterioids, azathioprine, cyclosporine and cyclophosphamide.[57,58]

Rapidly progressive disease and disease with extensive lung involvement usually needs treatment with either daily oral or monthly cyclophosphamide in combination with corticosteroids.[58]

Mild yet progressive disease is usually treated with azathioprine together with prednisolone. If toxicity is noted in the absence of expected response to treatment, then consideration should be given to stop treatment.[58] All patients with ILD should receive prophylaxis against pneumocystis jeroveci. A recent study has reported beneficial effects with mycophenolate mofetil.[59,60]

In patients whose lung disease has already progressed to extensive fibrosis, the therapeutic options are very limited. They usually show little response to immunosuppressive therapy, instead suffer from drug related toxicity. Hence, lung transplantation may be the only hope in these patients.

Drugs such as Rituzumab and TNFα inhibitors have not undergone rigorous trial for their usage in RA-ILD. Some studies have reported worsening of pulmonary status in patients taking TNFα inhibitors due to their pulmonary toxicity.[61,62,63]

UIP Vs NSIP : Response to treatment

It is not known whether there exists a difference in response to treatment between the two predominant histopathologic patterns – UIP and NSIP. The conclusion of a recent narrative review is that UIP responds poorly to treatment with corticosteroids.[54] But there is a need for further prospective studies to look upon the response to treatment among the different ILD patterns.

Treatment related toxicity

Treatment related lung injury can be caused by a number of therapeutic agents. Gold and penicillamine can induce diffuse alveolar damage, osteoporosis and bronchiolitis obliterans.[68,69] Methotrexate itself can induce varying patterns of interstitial pneumonia. RA patients treated with methotrexate can develop life threatening acute pneumonitis. Usual clinical features are dry cough or dyspnoea. The usual HRCT pattern observed in this

condition is patchy ground glass opacities with centrilobular nodules and lymphadenopathy. One useful investigation in this setting is BAL which usually shows lymphocytosis. Histology reveals interstitial fibrosis or pneumonia, small and ill defined granulomas and increased tissue eosinophils.[70] Methotrexate induced interstitial pneumonitis is mainly a diagnosis of exclusion, hence it is very important to rule out opportunistic infection or exacerbations of pre-existing interstitial pneumonia. Once diagnosed, treatment options are drug withdrawal and high dose corticosteroid therapy. The reported mortality in a recent study is 15%, hence close monitoring and early diagnostic measures such as BAL or lung biopsy are recommended during methotrexate treatment. A guideline for methotrexate therapy has been proposed recently.[71]

Prognosis of RA-ILD

As for as asymptomatic PFT abnormality is concerned, the clinical course of the disease was found to be stable without any increase in the PFT abnormality over a time period of ten years according to a longitudinal study.[64]

The disease can take either of two courses like a fulminant one or one with a slow progression. There is a wide variation in the reported two year mortality of RA-ILD patients ranging from 14% to 50%.[43,44] According to one study done on hospitalized patients with RA-ILD, the median survival was 3.5 years and the 5 year mortality rate was 50%.[65] When compared with idiopathic

pulmonary fibrosis (IPF), certain studies have reported a similar mortality rate,[66] whereas others have reported a higher survival among patients with RA-ILD.[58]

Prognostic significance – UIP Vs NSIP

When compared with NSIP pattern, there are many prognostic difference of significance in UIP pattern. Patients with UIP pattern in HRCT have heightened risk of progression, and are associated with bad prognosis and increased mortality.[53]

Approach to ILD in RA[67]

In a recent review (Eunice et al)[67] of the RA-ILD, authors have proposed the following clinical approach to patients with rheumatoid arthritis, with reference to ILD –

- All patients with RA should undergo annual screening for ILD that includes clinical history and examination to look for pulmonary signs and symptoms.
- X-ray – to be taken at the time of diagnosis of RA, and then alternate years thereafter. In long standing cases, annual chest x-ray is advised.
- When ILD is suspected, exclude alternative etiologies like ILD secondary to occupational and environmental exposures, medications, or the presence of concomitant secondary Sjogren syndrome. Serologic evaluation for the presence of auto antibodies (anti-SS-A/Ro and anti-SSB/ La) should be performed.

- Patients with suspected RA- ILD should undergo spirometry and diffusing capacity of the lung for carbon monoxide.
- HRCT scans are advocated in all patients suspected to have ILD. It has a high sensitivity for detecting RA-ILD and can predict the possible histopathological pattern and indirectly, the prognosis. Lung biopsy may be considered when HRCT is inconsistent.
- NSIP pattern needs aggressive treatment with pharmacologic therapy.
- UIP pattern indicates worse prognosis in which the ultimate option would be lung transplantation. Further research is needed on the role of pharmacologic therapy in this situation.

MATERIALS AND METHODS

Place of study

The study was conducted at **Coimbatore medical college hospital** during the period of **September 2010 to August 2011**.

Type of the study

It is a **cross sectional study.**

Study population

The study population consisted of consecutive patients with a definite diagnosis of **RA** (based on American rheumatism association criteria 1987) attending Rheumatology OPD, Coimbatore medical college hospital during the study period, with features suggestive of **ILD** (Pulmonary symptoms and signs) together with either or both of the following-

1. Suspicious interstitial attenuation pattern in chest x-ray.
2. ILD pattern in HRCT.

Inclusion criteria

1. Definite diagnosis of RA **(ACR criteria 1987).**
2. Pulmonary signs and symptoms together with radiological features consistent with ILD.
3. Age > 18 years.

Exclusion criteria

1. RA patients without pulmonary signs or symptoms.
2. Other connective tissue disorders.
3. Age < 18 years.
4. Pregnant and lactating women.
5. Sick patients unable to undergo PFT.
6. Pulmonary symptoms due to other chronic respiratory illnesses like infection, allergic alveolitis, pneumoconiosis etc..,

Methodology

The Coimbatore medical college hospital runs a rheumatology clinic every day. The subjects for this study were chosen from this clinic. Approval to conduct the study is obtained from the institute's ethical committee. All patients are included to the study only after obtaining informed consent from them.

Patients with the definite diagnosis of RA were initially screened clinically for pulmonary signs and symptoms of RA-ILD. All patients with clinical suspicion of ILD underwent chest imaging studies including X-ray and HRCT. Those with radiological evidence of ILD were included in the study as study subjects. All of the patients included in the study were receiving drug treatment according to the standard protocol.

A **detailed history** was taken using the standard proforma prepared for the study purpose. Proforma included collection of personal data, smoking

habits, duration of joint symptoms and pulmonary symptoms, previous respiratory illnesses if any, other addictions etc. The presence of pulmonary symptoms like cough with or without expectoration, dyspnoea, wheeze, chest pain and hemoptysis are noted. General symptoms like weight loss, fatigue, fever, anorexia were also noted. Then a detailed **physical examination** was carried out that include documentation of pallor, cyanosis, clubbing, pedal edema, respiratory signs including bibasilar crackles, tachypnea, rhonchi, features of heart failure etc.

Blood investigations were done in the patients, which includes complete hemogram, urine routine analysis, ESR, C – reactive protein and rheumatoid factor.

Radiological investigation

Patients were then subjected to radiological imaging (**chest x-ray and HRCT**). Chest x-ray patterns were described as normal, nodular, honeycombing, ground-glass and reticular patterns. HRCT was performed with 1mm thick sections at 10mm intervals. Reports were analyzed by two radiologists blinded to the study and the consensus report was taken as final. Patterns were described as pure reticular, pure ground-glass, mixed pattern, normal or other pattern such as emphysema, bronchiectasis, and consolidation.

Description of CT findings

- Reticular pattern – presence of intercepting lines with appearance varying from a fine network to frank honeycombing
- Ground-glass pattern – patchy or diffuse increase in lung density that did not obscure pulmonary vasculature
- Mixed – where ground-glass and reticulation are of equal proportions

The predominant lobe involved was also described.

Pulmonary function test was done within two weeks of HRCT scan. All patients underwent PFT according to the standard protocol and included spirometry and lung volumes. Measurements were expressed as percentage of value predicted for age, gender and height according to standardized tables. PFT patterns were classified as restrictive (mild / moderate / severe) abnormality, obstructive abnormality, mixed defect and normal pattern as described below -

Normal	-	FVC >80%, FEV1/FVC - 70 To80%
Mild restriction	-	FVC 60 TO 80%, FEV1/FVC >80%
Moderate	-	FVC 50 To 60%, FEV1/FVC >80%
Severe	-	FVC <50%, FEV1/FVC >80%
Obstructive	-	FVC >60%, FEV1/FVC < 70%
Mixed	-	FVC < 60%, FEV1/FVC < 70%

Broncho-alveolar lavage was done in 10 patients. In others, it was not done because 15 patients declined the procedure; five patients were excluded due to advanced disease and poor respiratory reserve. Cytological analysis was done for differential count and results were expressed as neutrophilic / lymphocytic alveolitis. Differential count was considered normal if values are as follows –

Non smokers: lymphocytes < 15%, neutrophils < 2%, eosinophils < 0.5%

Smokers: lymphocytes <10%, neutrophils < 4%, eosinophils < 1%

Statistical analysis

Analysis was done using Sofastat software. Continuous data were described as mean and standard deviation (mean +/- SD), and categorical variables as numbers. Comparisons between two categories were made using 2 tailed student t-test for continuous variables. To analyze categorical data, chi square test is performed. Pearson correlation is used to correlate the continuous variables like disease duration, HRCT patterns and pulmonary function test abnormalities.

RESULTS

During the study period, a total of 30 patients were included in the study, of age ranging from 36 years to 72 years.

Age distribution

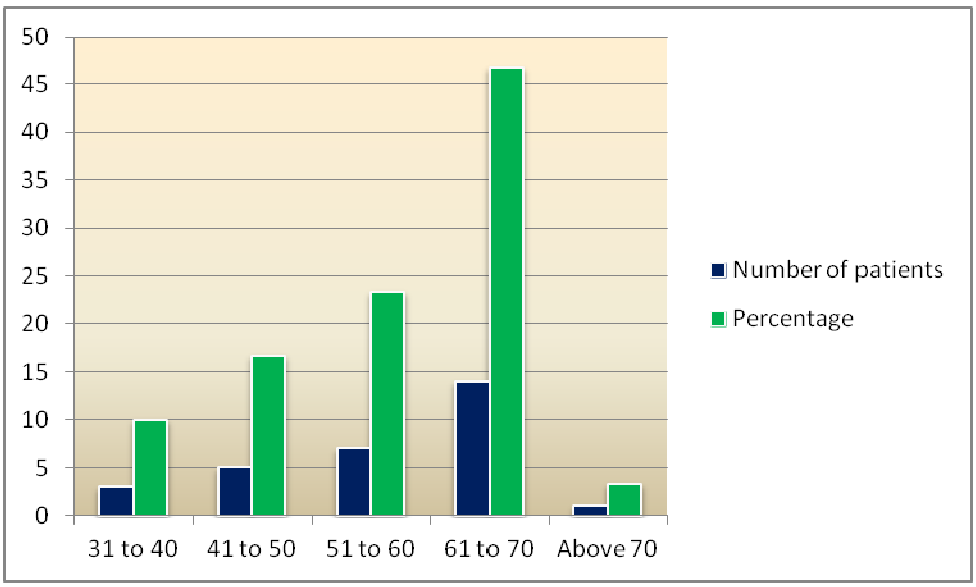
The mean age of patients with RA-ILD included in our study was **56.2 years** (range = 36 to 72 years). The most common age group affected in our study population was 61 to 70 years (14 patients or 46.7%), followed by age group of 51 to 60 years (7 patients or 23.3%). There was only 1 patient above the age group of 70 years constituting 3.3% of the total number of patients.

- Mean age of male patients = **59.1 years &** female patients = **54.2 years**

Table 1 – Age wise distribution of study population (n=30)

Age group (years)	Number of patients	Percentage
31 to 40	3	10
41 to 50	5	16.7
51 to 60	7	23.3
61 to 70	14	46.7
Above 70	1	3.3

Chart 1 – Age wise distribution of study population

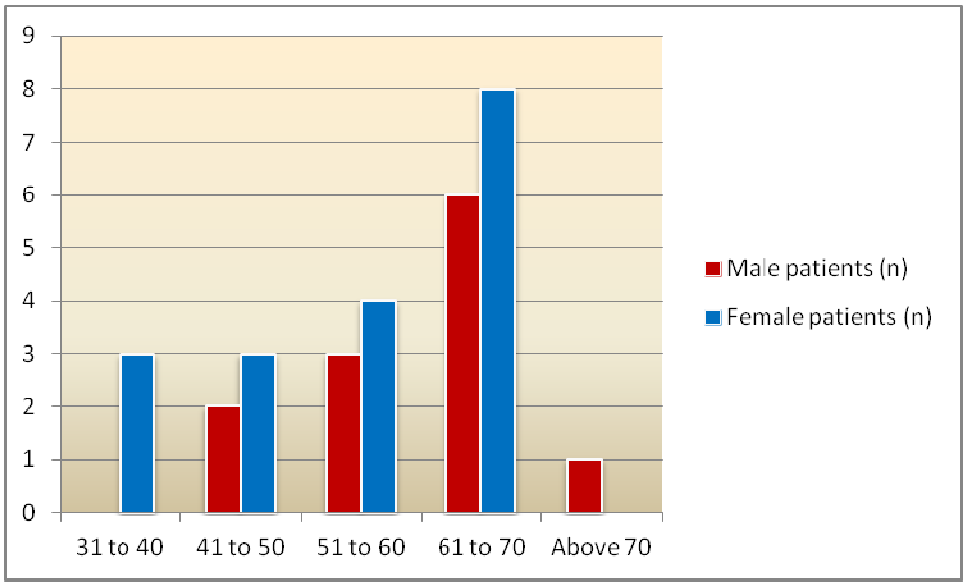


X axis – age group; Y axis – number of patients and percentage

Table 2 - Age group wise distribution of male and female patients

Age group (years)	Male patients (%)	Female patients (%)
31 to 40	0	3 (16.7)
41 to 50	2 (16.7)	3 (16.7)
51 to 60	3 (25)	4 (22.2)
61 to 70	6 (50)	8 (44.4)
Above 70	1 (8.3)	0

Chart 2 – age group wise distribution of gender

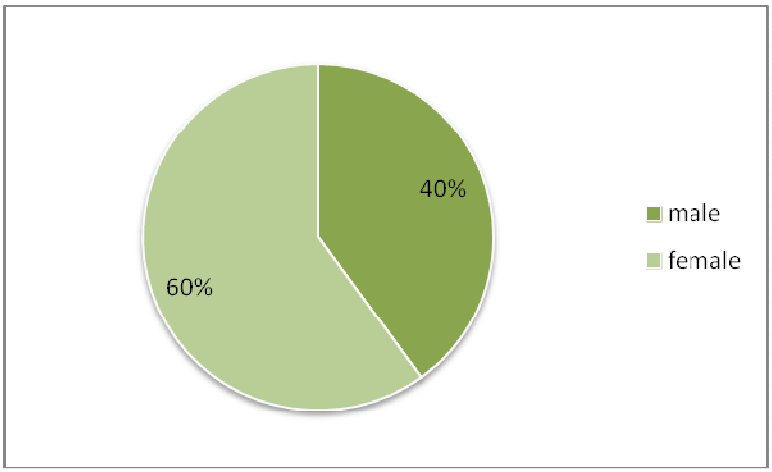


X axis = age group; Y axis = number of patients

Gender frequency

In our study, 60% of the study subjects (18 patients) were females and 40% of the population was male subjects (12 patients).

Chart 3 – Gender frequency



Smoking

11 out of 12 male subjects were smokers (36.7% of the total subjects). None of the female patients were smokers.

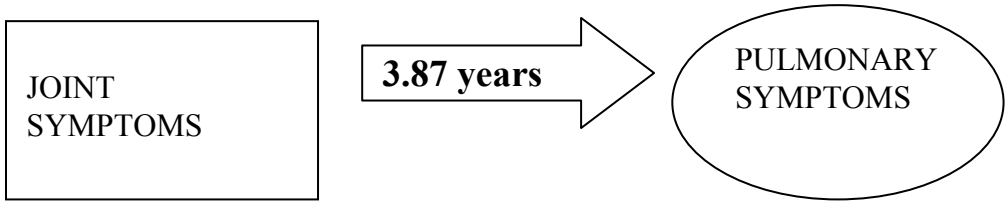
Joint symptoms and pulmonary symptoms

Among the study population, the mean duration of joint symptom was **7.03 years**, and mean duration of pulmonary symptom was **3.16 years**. Two patients (6.7%) had joint symptoms for less than 3 years, nine patients (30%) had joint symptoms for 3 to 6 years, ten patients (33.3%) had joint symptoms for 6 to 9 years and nine patients (30%) had symptoms over and above 9 years.

Table 3 – Duration of joint symptoms in patients

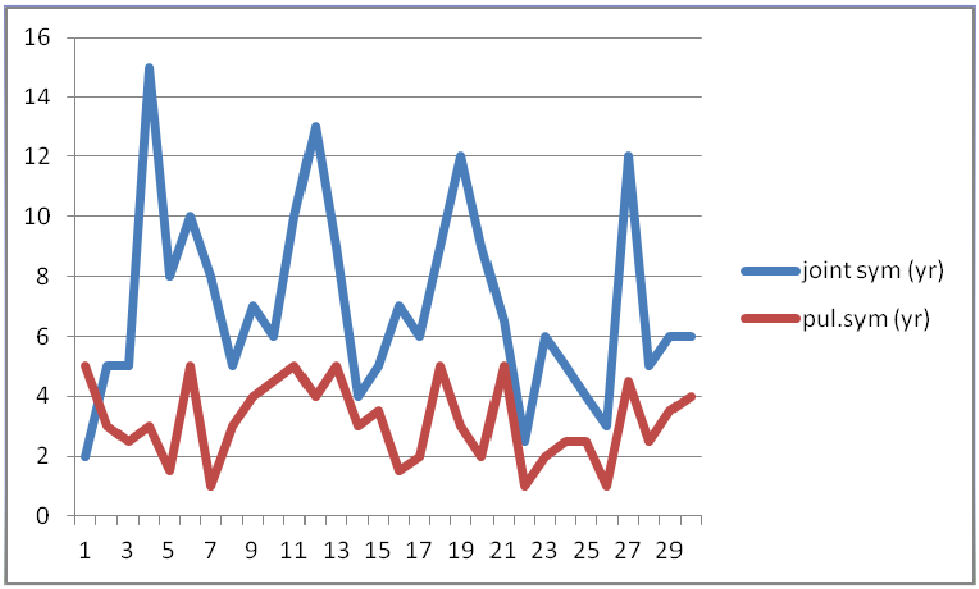
Duration of joint symptoms	Number of patients	Percentage (%)
Less than 3 years	2	6.7
3 to 6 years	9	30
6 to 9 years	10	33.3
More than 9 years	9	30

The average duration of joint symptoms after which the pulmonary symptoms begin to manifest was 3.87 years. There was considerable variation in the duration of pulmonary symptom ranging from one to five years. In all but one patient, joint manifestation preceded pulmonary complaints.



On an average, pulmonary symptoms developed after 3.87 years of joint symptoms in the study group.

Chart 4 - Relationship between occurrence of joint and pulmonary symptoms in the study population



X axis = individual patients; Y axis = number of years

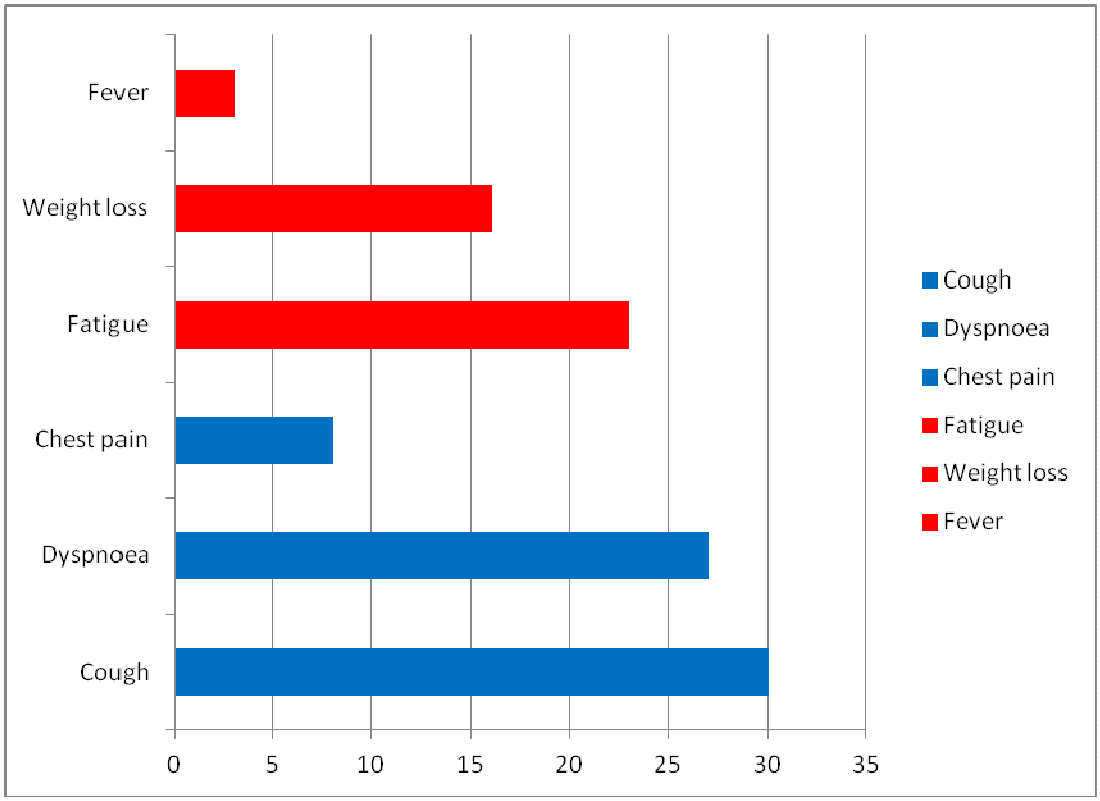
Frequency of pulmonary symptoms and general symptoms

In all patients, the symptom of cough appeared at some point of time during the course of their illness (100%), whereas dyspnoea was present in 27 patients (90%). When the presenting pulmonary symptom was analyzed, dyspnoea outnumbered cough as the predominant presenting pulmonary feature. Dyspnoea was the presenting complaint in 19 out of 30 patients (63.3 %) and cough was the presenting complaint in 11 out of 30 patients (36.6%). Chest pain was observed in eight of the thirty patients (26.6%) during the course of their illnesses. Apart from this, other general symptoms noted were fatigue, weight loss and fever as shown in the table.

Table 4 – Frequency of Pulmonary and general symptoms (n=30)

Symptoms	Number of patients	Percentage
Cough	30	100%
Dyspnoea	27	90%
Chest pain	8	26.6%
Fatigue	23	76.6%
Weight loss	16	53.3%
Fever	3	10%

Chart 5 - Frequency of pulmonary and general symptoms



X axis = number of patients

Respiratory signs

Among the physical examination findings, presence of bibasilar crackles was the most common finding (28 patients, 93.3%). Tachypnoea was present in 16 patients (53.3%) and rhonchi in 9 patients (30%). Clubbing was seen in 10 patients (33.3%)

Table 5 – Physical examination findings (n=30)

Respiratory sign	Number of patients	Percentage (%)
Bibasilar crackles	28	93.3
Tachypnoea	16	53.3
Rhonchi	9	30
Clubbing	10	33.3

Blood investigations

- Anemia was found in 23 patients (76.7%).
- An elevated ESR of more than 30 at one hour was found in 27 patients (90%), whereas 16 patients had ESR more than 60.
- CRP was positive in 24 patients (80%).
- Rheumatoid factor was positive in 23 patients (76.7%) of the total subjects.

Table 6 - Laboratory findings (n=30)

Investigation	Number of patients	Percentage
Anemia	23	76.7%
ESR > 30	27	90%
ESR > 60	16	53.3%
Positive CRP	24	80%
Positive RA factor	23	76.7%

Radiography

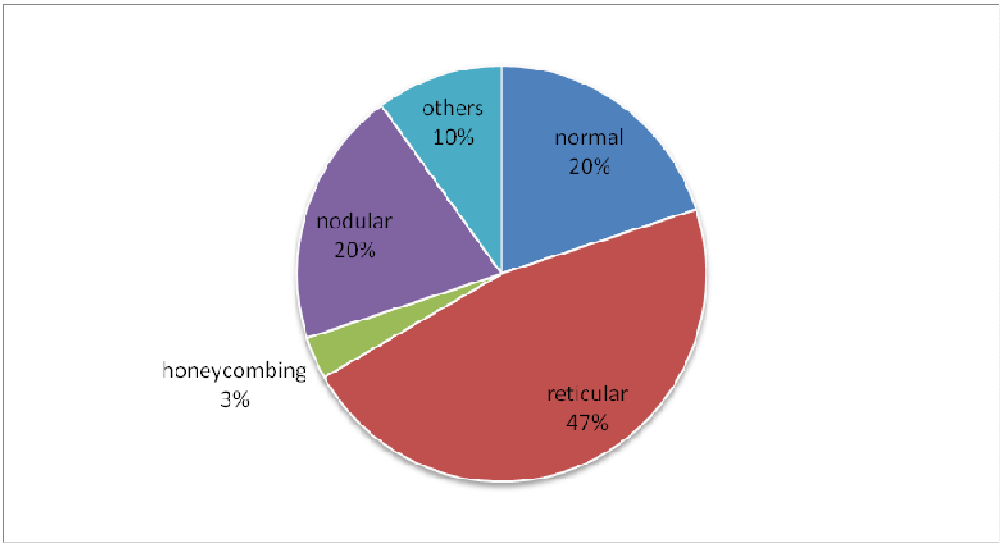
X-ray appearance

In our study, six patients (20%) had normal x-ray appearance. Fourteen (46.7%) patients showed reticular pattern which was the most common x-ray appearance. One patient had honeycombing appearance in x-ray (3.3%). Six patients (20%) had nodular opacities. Three patients (10%) had findings such as bronchiectasis and pleural thickening. None of the patients had pleural effusion. Thereby, nine out of thirty patients (30%) showed x-ray appearance inconsistent with ILD.

Table 7 – X-ray appearance (n=30)

X-ray pattern	Number of patients	Percentage
Reticular	14	46.7
Honeycombing	1	3.3
Nodular	6	20
Others	3	10
Normal	6	20
Total	30	100

Chart 6 showing x-ray appearances in 30 patients



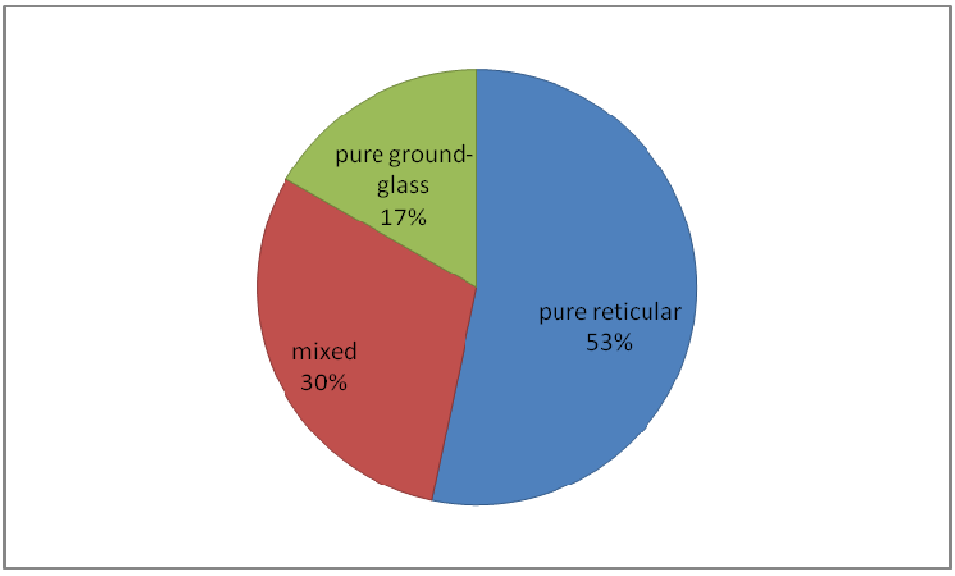
HRCT pattern

In our study, all patients showed features suggestive of ILD in HRCT. Three different patterns were identified such as pure reticular, pure ground-glass and mixed pattern. Sixteen patients (53.3%) showed reticular pattern, five patients (16.7%) showed ground-glass pattern and nine patients (30%) showed mixed pattern. Thereby, reticular pattern was the predominant HRCT pattern followed by mixed pattern. Honeycombing appearance was seen in five patients. As it represents late stage of reticular pattern, it was counted along with reticular pattern. Four patients showed bronchiectactic changes along with other ILD findings. Bilateral lower lobe was the most common lobes to be involved (28 patients out of 30, 93.3%)

Table 8 - showing frequency of HRCT pattern

HRCT pattern	Number of patients	Percentage
Reticular	16	53.3
Ground-glass	5	16.7
Mixed	9	30
Total	30	100

Chart 7 showing HRCT patterns found in the study



Pulmonary function test

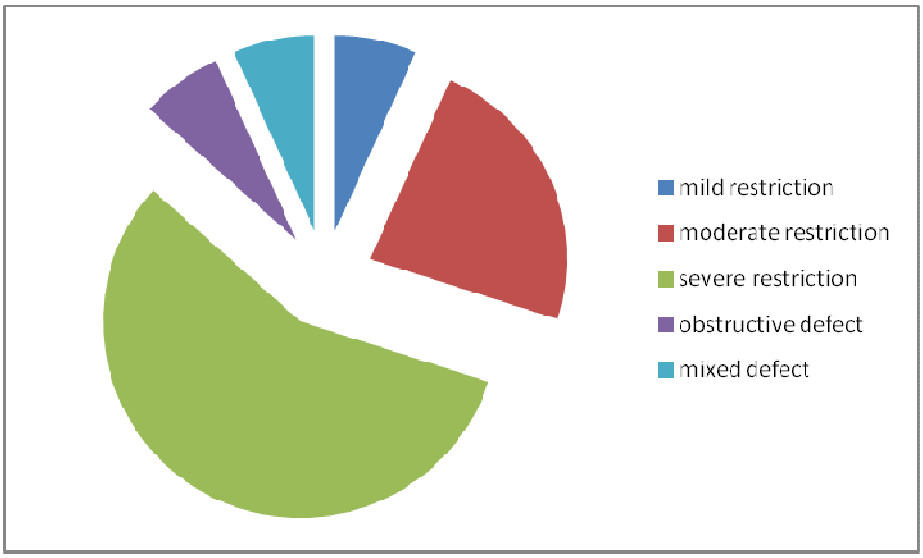
All patients underwent pulmonary function test within two weeks of HRCT as part of our protocol. Most of the patients (26 out 30, 86.6%) showed restrictive pattern in PFT. Two patients showed obstructive pattern (6.7%) in

PFT and the remaining two (6.7%) showed mixed defect in PFT. Among the patients with restrictive abnormality in PFT, seventeen patients (56.7%) had severe restriction. Seven patients (23.3%) had moderate degree of restriction in PFT. Two patients (6.7%) had mild restriction.

Table-9 showing pulmonary function abnormality in the study population

PFT abnormality	Number of patients	Percentage
Severe restriction	17	56.7
Moderate restriction	7	23.3
Mild restriction	2	6.7
Obstructive	2	6.7
Mixed	2	6.7
Total	30	100

Chart 8 - showing pulmonary function test abnormality (PFT)



Broncho-alveolar lavage (BAL)

Five out of ten patients (50%) in whom BAL was done, showed neutrophilic alveolitis. Two (20%) showed lymphocytic alveolitis. Three patients (30%) had their BAL pattern within normal limits. Four out of five patients with ground-glass pattern (80%) showed neutrophilic alveolitis in BAL.

Smoking Vs HRCT

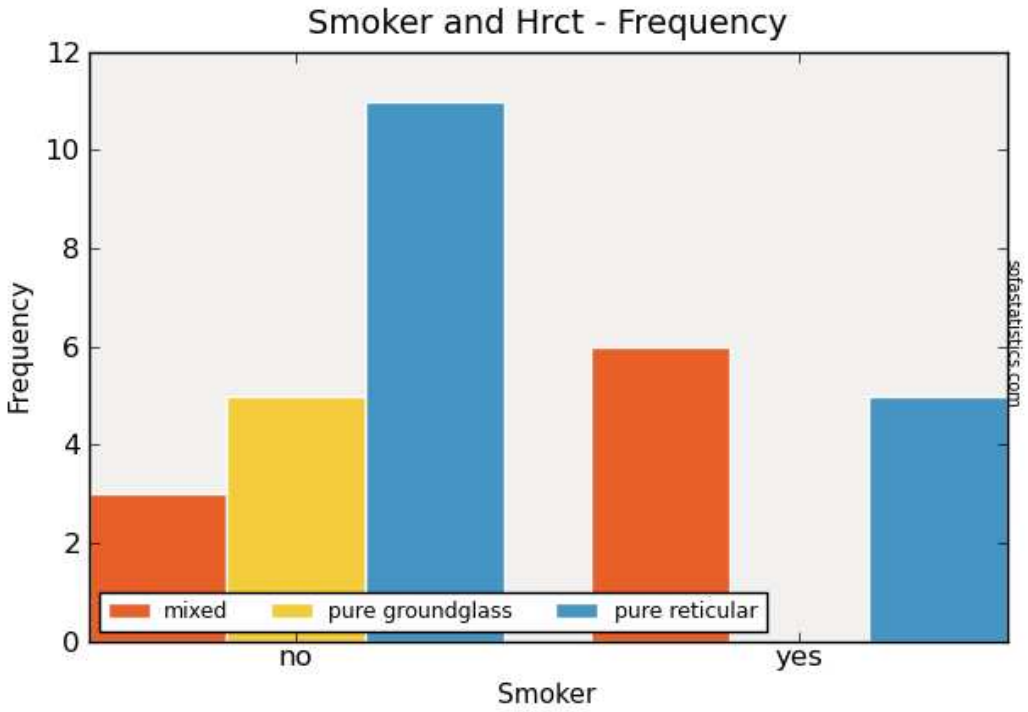
Out of the 11 smokers, none had a ground-glass pattern in HRCT, five persons had reticular pattern and six persons had mixed pattern.

Table 10 showing relation of smoking history to HRCT

		Smoking	
		Yes	No
HRCT	Reticular	5	11
	Ground-glass	0	5
	Mixed	6	3
	Total	11	19

p- value = 0.037

Chart 9 showing relation between smoking habit and HRCT pattern



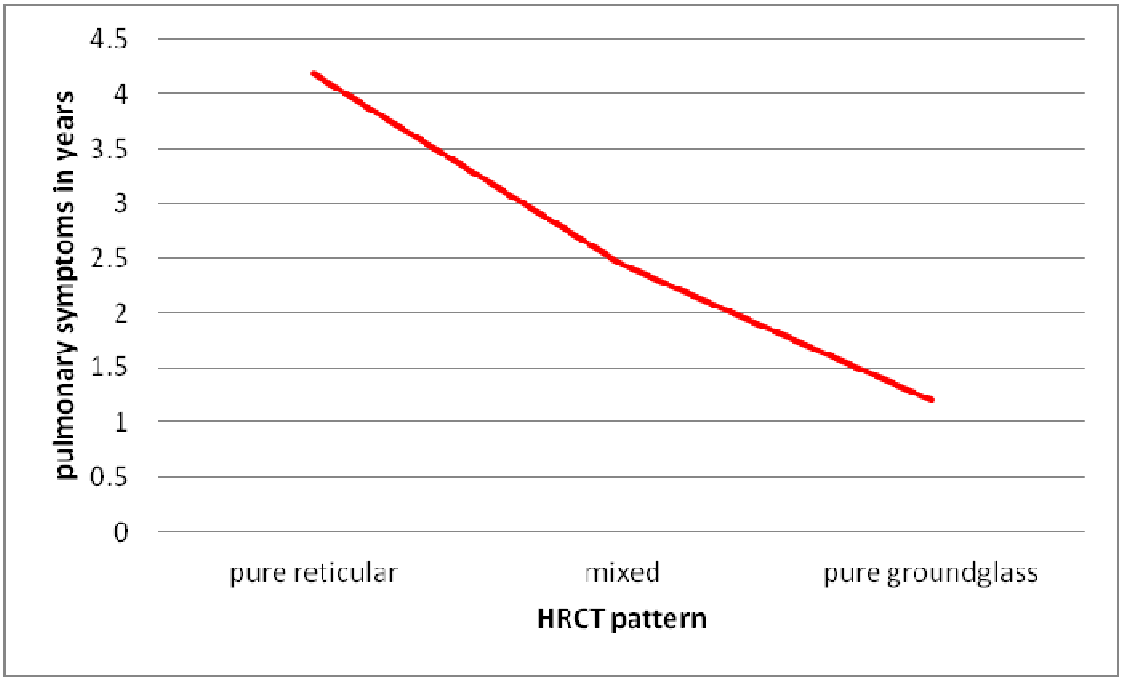
Relationship between pulmonary symptom duration and HRCT pattern

For patients who showed predominant reticular pattern in HRCT, the average duration of pulmonary symptoms was **4.19 years**, as compared to patients with predominant ground glass pattern in HRCT, for whom the average duration of pulmonary symptoms was **1.2 years**. The difference between the mean duration of symptoms between the two populations (reticular pattern in HRCT Vs ground-glass pattern in HRCT) was statistically significant as shown in the following table 11.

Table 11 – Duration of pulmonary symptoms and HRCT pattern

HRCT pattern	Duration of pulmonary symptoms
Predominant reticular pattern	4.19 years*
Predominant ground-glass pattern	1.2 years*
P value – 0.0001; Confidence interval = 2.22 to 3.75 (95%)	

Chart 10 - showing that ground-glass pattern is an earlier HRCT finding compared with reticular which in most cases a late finding



HRCT pattern and pulmonary function test

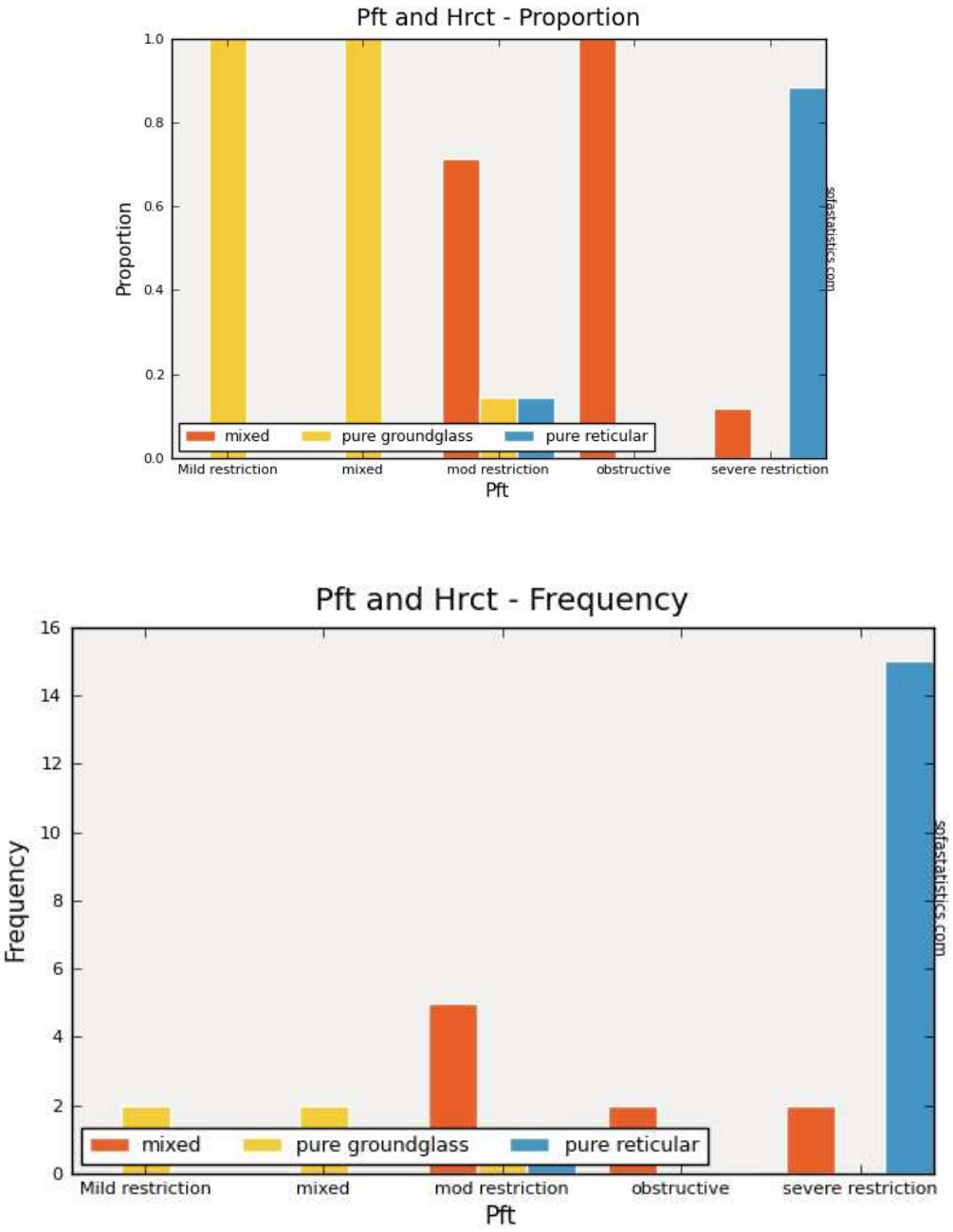
Among the three different patterns of HRCT findings in our study subjects, **reticular pattern** was more commonly associated with **severe restriction** in pulmonary function test, and was statistically significant.

Table 12- showing relation between HRCT pattern and PFT findings

		HRCT							
		Reticular		Mixed		Ground-glass		Total	
		obs	exp	obs	exp	obs	exp	obs	exp
PFT	Mild	0	1.1	0	0.6	2	0.3	2	2
	Mod	1	3.7	5	2.1	1	1.2	7	7
	Severe	15	9.1	2	5.1	0	2.8	17	17
	mixed	0	1.1	0	0.6	2	0.3	2	2
	obstructive	0	1.1	2	0.6	0	0.3	2	2
	total	16	16	9	9	5	5	30	30

p value: < 0.001
Pearson's Chi Square statistic: 39.297

Chart 11 - showing relation between HRCT finding and PFT abnormality



The **mean FVC%** among patients showing pure reticular pattern in HRCT was **20.18**, whereas it was **51.4** in patients with pure ground-glass pattern. This finding was statistically significant.

Table 13 - FVC comparison between pure reticular and pure ground-glass

Group	Number	Mean FVC%	SD	Min FVC	Max FVC
Reticular	16	20.188	10.055	13	56
Ground-glass	5	51.4	10.383	40	65.0

p-value < 0.001

Chart 12 showing FVC to HRCT association

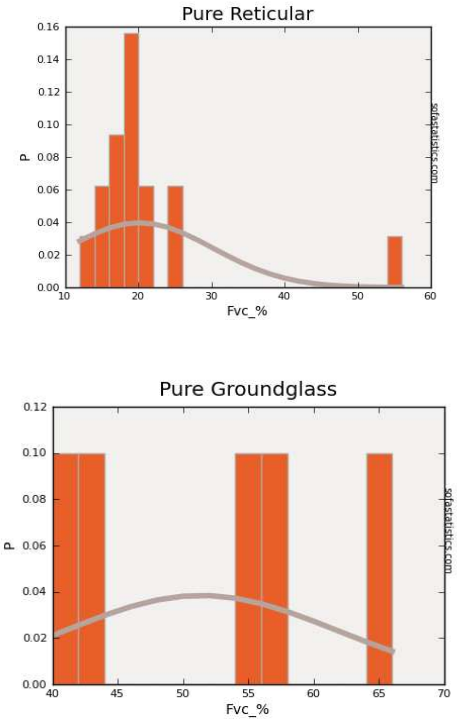
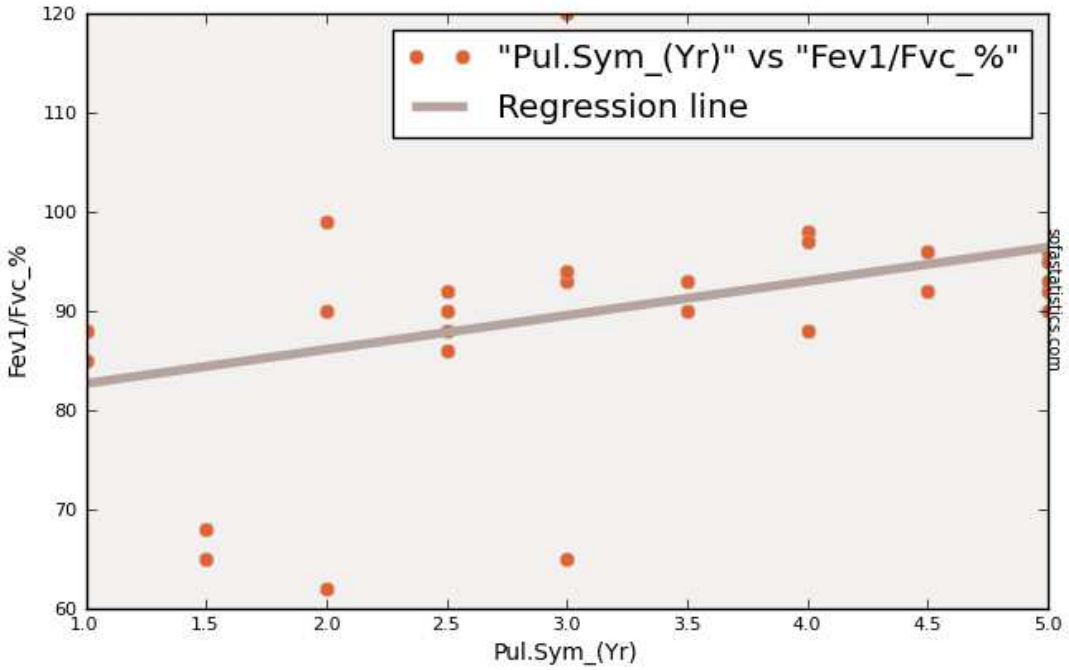


Chart 13 - Correlation between duration of pulmonary symptom & FEV1/FVC ratio



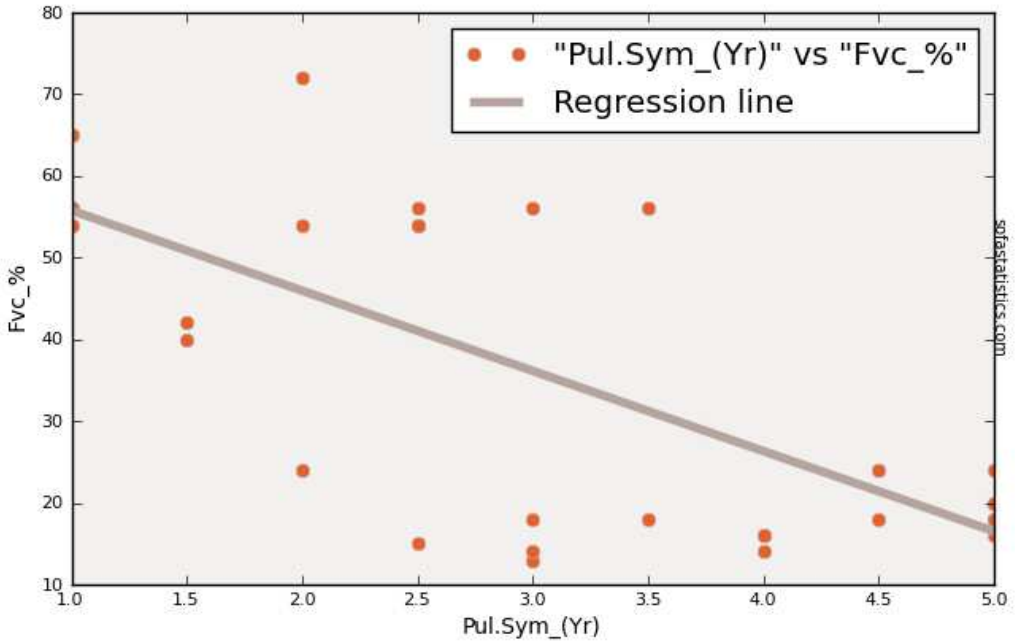
Two-tailed p value: 0.046

Pearson's R statistic: 0.367

Slope: 3.432

Inference = There was a linear correlation between duration of pulmonary symptom and FEV1/FVC ratio

Chart 14 - Correlation between duration of pulmonary symptom & FVC %



Two-tailed p value: < 0.001

Pearson's R statistic: -0.647

Slope: -9.813

Inference = There was a negative correlation between duration of pulmonary symptom & FVC %

X-ray versus HRCT

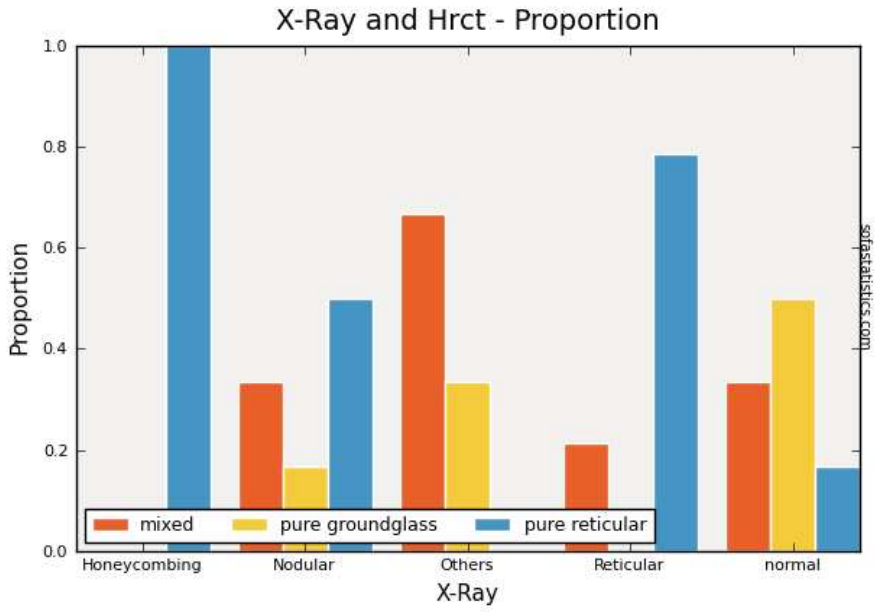
When the agreement between X-ray and HRCT was tested, it was not statistically significant, even though most of the patients with x-ray finding of reticular pattern had a similar pattern in HRCT.

Table 14 - X-ray versus HRCT

		HRCT					
		Mixed		Ground – Glass		Reticular	
		Obs	Exp	Obs	Exp	Obs	Exp
X-ray	Honeycomb	0	0.3	0	0.2	1	0.5
	Nodular	2	1.8	1	1.0	3	3.2
	Others	2	0.9	1	0.5	0	1.6
	Reticular	3	4.2	0	2.3	11	7.5
	Normal	2	1.8	3	1.0	1	3.2
	Total	9	9	5	5	16	16

p-value = 0.076

Chart 15 - X-ray versus HRCT



Other results

We tested the associations between the following variables but found to be statistically not significant.

- Rheumatoid factor and HRCT finding; p value = 0.312
- Age versus FEV1/FVC; p-value = 0.845
- Age versus FVC%; p-value = 0.182
- Joint symptom duration versus HRCT; p-value=0.156
- Smoking versus PFT; p-value=0.207

SUMMARY OF RESULTS

- A total of 30 patients comprising 18 females and 12 males with mean age of 56.2 years were included.
- Mean duration of joint symptom was 7.03 years & pulmonary symptom was 3.16 years. The average duration of joint symptoms after which the pulmonary symptoms begin to manifest was 3.87 years.
- Dyspnoea was the most common presenting symptom (19 patients or 63.3%), followed by cough (11 patients or 36.6%).
- Bibasilar crackles were the most common pulmonary sign (28patients or 93.3%).
- RA factor was positive in 23 patients (76.6%)
- Reticular pattern was the predominant radiological finding in both X-ray (46.7%) and HRCT (53.3%).
- Nine patients (30%) with no evidence of ILD in X-ray had ILD findings in HRCT. Most patients (86.6%) showed restrictive abnormality in PFT.
- Neutrophilic alveolitis was seen in 5 out of ten patients who underwent BAL.

DISCUSSION

Indian study on RA-ILD[81]

There is very little Indian literature on ILD in RA. In a study done at Baroda, authors have concluded that 36% of RA have ILD. HRCT was more sensitive than X-ray and spirometry in diagnosing ILD in RA.

Average age and duration of illness

In our study, we have included patients of RA-ILD ranging from 36 to 72 years. Among the study subjects, the most common age group was between 61 to 70 years. Studies[20] that have looked into the extra articular manifestations of RA, have reported that these are common between 50 to 60 years. In studies focusing on RA-ILD, the most common age group reported to be affected by RA-ILD is around 60 years[44, 62, 63]

Table 15 – Average age & duration of illness compared with other studies

Study	Average age in years	Average disease course (months)
Biederer et al[44]	61	123
Muller – Leisse et al[62]	61	144
Remy-Jardin et al[63]	57	144
Hakala et al[65]	64	180
Our study*	56.2	84

The common age group affected by RA-ILD, in our population is similar to the one reported elsewhere (see table). In our study, female patients had an earlier onset (54.2years) when compared to male patients (59.1 years).

Several studies have reported longstanding RA as a risk factor for ILD[28,30]. In our study, the mean duration of joint symptom was 7.02 years and 63.3% of the study population had more than 6 years of joint symptoms.

Gender distribution

Even though, most of previously done studies show male predominance of RA-ILD[72, 73], there are few studies such as Tanaka et al in 2004[45] showing female predominance like our study.

ILD as the presenting manifestation

Previous studies have reported that joint symptoms precede pulmonary symptoms in majority of the patients with RA-ILD[74]. However Lee HK et al.[36] in their study have found out that they can occur simultaneously or pulmonary symptoms can occur earlier than joint symptoms, especially in NSIP pattern. Similar results were reported in studies done by Fujita J, et al.[38] and Sato T, et al[39].

Even though, in our study, **only one patient (3.3 %) presented with pulmonary symptom**, previous studies have reported that up to 20% of patients with RA can have pulmonary symptom as the initial presentation[75], hence forth

we advocate considering underlying CTDs as a possible cause in all ILD patients.

ILD – an early extra articular manifestation of RA

Our study has shown that on an average, pulmonary symptoms developed **3.87 years** after joint symptoms. This suggests that **ILD can be a relatively early extra articular manifestation of RA.** We advocate active surveillance for development of ILD in all patients with RA. In a study by Gabbay et al done on recent onset RA patients (<2years), 58% had ILD[28], detected during the study, thereby reinforcing the above recommendation.

Most commons

The most common respiratory symptom in our study was **cough** (100%). The most common presenting symptom was **dyspnoea**. The most common general symptom was fatigue. The most common respiratory sign was **bibasilar fine crackles**. These findings were consistent with the literature[76].

Clubbing was present in one third of the patients (10 out of 30 patients, 33.3%). Similar to our finding, it has been noticed in the past that, in comparison with idiopathic pulmonary fibrosis, clubbing is less common in RA-ILD[55].

Lab parameters

Prevalence of **RA factor** in the study group was **76.7%** comparable with the estimated prevalence. Acute phase reactants were elevated in more than 80% of patients. Anemia was noted in three fourth of the patients.

Role of radiological investigations in RA-ILD

It is a known fact that **X-ray is an insensitive tool to diagnose RA-ILD**[76,77]. In our study too, we have noticed that in nine patients (30%), X-ray missed a diagnosis of ILD which was picked up by HRCT.

HRCT is highly sensitive for detecting the presence of ILD and it is abnormal in up to 80% of clinically suspected RA-ILD.[78]

HRCT characteristics of the study population

a. The predominant HRCT pattern was reticular (53.3%).
b. Ground-glass pattern was seen in 16.7%.
c. The most common lobe involved was bilateral lower lobe.
d. Reticular pattern was associated with longer duration of illness, whereas ground-glass opacity was seen in patients with shorter duration illness.
e. Bronchial abnormalities like bronchiectasis were present in 13.3%
f. Nodular opacity and honeycombing were seen in 16.7% each

In the literature available until now, reticular pattern with or without honeycombing is a major abnormality and is more common than ground-glass

opacity.[30,32,43,52] Also, it has been previously noted that ground-glass pattern is common during early part of the disease.[28,52]

Previous studies have shown that reticular pattern in HRCT is irreversible[77] and corresponds to UIP pattern in histopathology (HP) and ground-glass pattern in HRCT corresponds to NSIP pattern.[36,45] UIP pattern in HP has a uniformly bad prognosis, whereas NSIP has good prognosis. So, in our study, there is a considerable population of patients **(46.7%)** with either pure ground-glass or mixed pattern in HRCT, **representing a potentially treatable population**. The remaining 53.3% of patients with pure reticular pattern may respond poorly to immunosuppressive therapy[54] and may need lung transplantation ultimately which is farfetched in our setup.

Smoking Vs HRCT

There were 11smokers in our study, in whom six showed reticular pattern and five showed mixed pattern, none had ground-glass pattern which carries good prognosis. Ground-glass pattern was seen only in non smokers. The association was statistically significant. It is a significant finding that **smokers have a high chance of harboring ILD with poor prognostic features (reticular).**

Pulmonary function test (PFT)

As expected, most of our patients had **restrictive** abnormality in PFT (**86.7%**). This has been previously reported in studies by Dawson JK, et al[30] and

Banks J, et al.[79] Also there was positive correlation between duration of pulmonary symptoms with FEV1/FVC ratio and negative correlation of pulmonary symptom duration with FVC% indicating that ILD worsens with advancing years.

A novel finding in our study is that most patients with severe restriction in PFT had reticular HRCT pattern, the two patients with mild restriction in PFT had ground-glass pattern in HRCT and most patients with moderate restriction of lung function in PFT had mixed pattern in HRCT. At a glance, it looks like PFT abnormalities are directly linked to HRCT patterns. Possible explanation would be that, most patients with ground-glass appearance in HRCT had shorter duration of illness and thereby lesser degree of extent of disease and hence producing a milder PFT abnormality as compared to patients with reticular pattern in whom the disease existed for longer duration. We recommend serial CT and PFTs to establish a relation between these two.

Broncho-alveolar lavage (BAL)

As part of our study, we did BAL in 10 patients. Fifteen patients declined the procedure and five patients were excluded due to advanced disease. Fifty percent of total patients in whom BLA was done and eighty percent of the patients with ground-glass appearance in HRCT showed **neutrophilic alveolitis** in BAL, in par with other studies.[52,56,57]

CONCLUSION

1. Interstitial lung disease associated with rheumatoid arthritis (RA-ILD) affects men and women in their late middle age.
2. RA-ILD can present within few years of occurrence of joint symptoms.
3. The treating physician should actively look for development of respiratory signs and symptoms in a patient with rheumatoid arthritis.
4. HRCT is the most useful test in evaluating suspected patients of RA-ILD as X-ray alone in an insensitive tool.
5. Reticular pattern is the most common HRCT finding in RA-ILD which indicates advanced disease.
6. Ground-glass appearance in HRCT signifies early disease and warrants aggressive treatment as it is potentially reversible.
7. Pulmonary function test is a useful tool in assessing the severity of RA-ILD and complements HRCT in diagnosis and management of RA-ILD.

SUMMARY

Objective –

1. To describe the clinical features, laboratory profile, radiographic patterns, pulmonary function tests abnormalities and broncho-alveolar lavage cytology of patients with RA-ILD.
2. To find out whether these investigations correlate with each other.

Methodology –

- Patients with the definite diagnosis of RA attending rheumatology clinic were screened clinically for pulmonary signs and symptoms of RA-ILD.
- All patients with clinical suspicion of ILD underwent chest imaging studies including X-ray and HRCT.
- Those with radiological evidence of ILD formed the study population. They were subjected to pulmonary function test and broncho-alveolar lavage along with other blood investigation. Their clinical, radiological and spirometry characteristics were noted and analyzed.

Results –

- A total of 30 patients comprising 18 females and 12 males with mean age of 56.2 years were included.
- Mean duration of joint symptom was 7.03 years & pulmonary symptom was 3.16 years. The average duration of joint symptoms

after which the pulmonary symptoms begin to manifest was 3.87 years.

- Dyspnoea was the most common presenting symptom (19 patients or 63.3%), followed by cough (11 patients or 36.6%).
- Bibasilar crackles were the most common pulmonary sign (28patients or 93.3%).
- 23 patients (76.7%) had positive RA factor.
- Reticular pattern was the predominant radiological finding in both X-ray (46.7%) and HRCT (53.3%).
- Nine patients (30%) with no evidence of ILD in X-ray had ILD findings in HRCT.
- Most patients (86.6%) showed restrictive abnormality in PFT.
- Neutrophilic alveolitis was seen in 5 out of ten patients who underwent BAL.

Conclusion –

- Interstitial lung disease associated with rheumatoid arthritis (RA-ILD) affects men and women in their late middle age, and can present within few years of occurrence of joint symptoms.
- HRCT is the most useful test in evaluating suspected patients of RA-ILD compared to X-ray. Pulmonary function test is useful in assessment and follow up of these patients.

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PROFORMA

Name Age/sex Occupation

Residence OP/IP no -

Smoker – Yes / No

Duration – joint symptoms ____yrs pulmonary symptoms ____yrs

Presenting respiratory symptom – cough / dyspnoea / wheeze / chest pain / hemoptysis

Other respiratory symptoms - cough / dyspnoea / wheeze / chest pain / hemoptysis

General symptoms – weight loss / fatigue / fever / others

Physical examination – pallor / cyanosis / clubbing / pedal edema / others

Pulse = _____ / min BP = _____ mmHg RR = _____ / min

RS examination – tachypnoea / rhonchi / crackles / consolidation / pleural effusion / others

CVS examination – ↑JVP / loud P2 / cardiac murmur / pericardial rub

_____

Lab results – CBC = Hb – gm/dL; TC – DC – platelet –

ESR – CRP – RA factor –

Blood urea – S.creatinine – RBS – S.Br –

SGOT – SGPT – S. ALP –

Urine routine –

Imaging studies –

CXR = normal / reticular / nodular / honeycombing / others

HRCT = normal / pure reticular / pure ground-glass / mixed

Pulmonary function test =

FEV1 / FVC =

FVC % =

Pattern = restriction (mild / moderate / severe) / obstruction / mixed

Bronchoalveolar lavage = normal / lymphocytic / neutrophilic

Notes _____

MASTER CHART

s. no	Age	agegroup	gender	smoker	joint sym (yr)	pul.sym (yr)	presenting symptom	other sym	gen symp	pulm signs
1	38	31 to 40	F	no	2	5	cough	2, 4	1	1,2,5
2	62	61 to 70	F	no	5	3	dyspnoea	1	1,2	1,2
3	68	61 to 70	M	yes	5	2.5	dyspnoea	1	2,3	2
4	63	61 to 70	F	no	15	3	dyspnoea	1	1,2	1,2,3
5	45	41 to 50	F	no	8	1.5	dyspnoea	1	1	1,2,3
6	42	41 to 50	F	no	10	5	dyspnoea	1	0	2
7	66	61 to 70	F	no	8	1	dyspnoea	1	1	1,2,3,5
8	62	61 to 70	M	yes	5	3	cough	0	2	2
9	48	41 to 50	F	no	7	4	dyspnoea	1,4	1	1,2,5
10	65	61 to 70	F	no	6	4.5	cough	2	1,2	1,2,5
11	36	31 to 40	F	no	10	5	dyspnoea	1,4	1	1,2
12	62	61 to 70	F	no	13	4	cough	2	1,2	2
13	64	61 to 70	M	yes	9	5	cough	2,4	2	2,3
14	42	41 to 50	M	no	4	3	dyspnoea	1	1	1,2,3,5
15	61	61 to 70	M	yes	5	3.5	dyspnoea	1,3	1,2	2,3
16	38	31 to 40	F	no	7	1.5	dyspnoea	1,4	1,2	1,2,3
17	61	61 to 70	M	yes	6	2	dyspnoea	1	1,2	2,3
18	63	61 to 70	F	no	9	5	dyspnoea	1,3	0	2
19	41	41 to 50	M	yes	12	3	dyspnoea	1	1,2	1,2,5
20	72	above 70	M	yes	9	2	dyspnoea	1,4	1	1,2,5
21	52	51 to 60	F	no	6.5	5	dyspnoea	1,3	1	1,2
22	56	51 to 60	F	no	2.5	1	cough	4	1	2
23	64	61 to 70	M	yes	6	2	cough	2,4	2	1,2
24	57	51 to 60	M	yes	5	2.5	dyspnoea	1	1,2	1,2
25	64	61 to 70	F	no	4	2.5	cough	2	1,3	2,5
26	57	51 to 60	F	no	3	1	cough	0	2	2
27	62	61 to 70	F	no	12	4.5	dyspnoea	1	1,3	1,2,5
28	58	51 to 60	F	no	5	2.5	cough	2	1,2	2,3
29	59	51 to 60	M	yes	6	3.5	dyspnoea	1	1	2,5
30	58	51 to 60	M	yes	6	4	cough	2	1,2	2

s. no	anemia	ESR	CRP	RF	X-RAY	HRCT	lobe involved
1	yes	< or=30	negative	negative	Reticular	pure reticular	
2	yes	31 to 60	positive	positive	Nodular	mixed	1,2,4
3	yes	61 to 90	positive	positive	normal	mixed	3,6
4	yes	61 to 90	positive	positive	Reticular	pure reticular	3,6
5	no	31 to 60	positive	positive	Others	pure groundglass	3,6
6	no	61 to 90	positive	positive	Reticular	pure reticular	3,6
7	yes	31 to 60	positive	positive	normal	pure groundglass	2,3,6
8	yes	61 to 90	positive	positive	Others	mixed	3,6
9	yes	61 to 90	positive	positive	Reticular	pure reticular	3,6
10	yes	61 to 90	positive	positive	Nodular	pure reticular	2,3,6
11	yes	61 to 90	positive	positive	Nodular	pure reticular	2,3,6
12	yes	61 to 90	positive	positive	Reticular	pure reticular	3,6
13	yes	61 to 90	positive	positive	Nodular	pure reticular	3,6
14	yes	< or=30	negative	negative	normal	pure reticular	2,3,6
15	yes	61 to 90	positive	positive	Reticular	pure reticular	3,6
16	no	61 to 90	positive	positive	normal	pure groundglass	3,6
17	yes	31 to 60	positive	positive	Nodular	mixed	1,2,4
18	no	61 to 90	positive	positive	Reticular	pure reticular	3,6
19	yes	61 to 90	positive	positive	Reticular	pure reticular	3,6
20	yes	31 to 60	positive	positive	Reticular	mixed	2,3,6
21	yes	61 to 90	positive	positive	Honeycombing	pure reticular	3,6
22	yes	< or=30	negative	negative	normal	pure groundglass	3,6
23	yes	31 to 60	positive	positive	Others	mixed	3,6
24	yes	31 to 60	negative	negative	Reticular	mixed	3,5,6
25	no	31 to 60	negative	negative	Reticular	mixed	2,3,6
26	no	31 to 60	positive	negative	Nodular	pure groundglass	3,6
27	yes	61 to 90	positive	positive	Reticular	pure reticular	3,6
28	yes	31 to 60	negative	negative	normal	mixed	3,6
29	yes	31 to 60	positive	positive	Reticular	pure reticular	3,6
30	no	61 to 90	positive	positive	Reticular	pure reticular	3,6

s. no	FEV1/FVC %	FVC %	PFT	BAL	X-RAY finding if category is others	other CT finding
1	92	16	severe restriction	normal	nil	nil
2	93	56	mod restriction	not done	nodularity	nodularity
3	92	15	severe restriction	not done	diffuse reticular	Traction bronchiectasis
4	120	13	severe restriction	not done	nil	honeycombing
5	65	40	mixed	Neu.alveolitis	bronchiectasis	nil
6	95	18	severe restriction	not done	nil	honeycombing
7	85	65	Mild restriction	Neu.alveolitis	nil	nil
8	65	70	obstructive	normal	bronchiectasis	reticular & ground glass
9	98	14	severe restriction	not done	nil	nil
10	92	18	severe restriction	not done	nil	nodularity
11	90	24	severe restriction	not done	nil	honeycombing
12	88	16	severe restriction	not done	nil	nil
13	96	20	severe restriction	not done	nil	nil
14	94	18	severe restriction	not done	nil	nodularity
15	93	18	severe restriction	lym alveolitis	diffuse reticular	traction bronchiectasis
16	68	42	mixed	normal	nil	nil
17	90	54	mod restriction	not done	nodular	traction bronchiectasis,
18	93	20	severe restriction	not done	nil	nil
19	116	14	severe restriction	lym alveolitis	nil	
20	99	24	severe restriction	not done	nil	nil
21	95	18	severe restriction	Neu.alveolitis	nil	honeycombing
22	88	54	Mild restriction	Neu.alveolitis	nil	nil
23	62	72	obstructive	not done	bronchiectasis	bronchiectasis
24	86	56	mod restriction	not done	nil	nil
25	90	54	mod restriction	not done	nil	nil
26	88	56	mod restriction	Neu.alveolitis	nil	nodularity
27	96	24	severe restriction	not done	nil	nil
28	88	54	mod restriction	not done	nil	nil
29	90	56	mod restriction	not done	nil	nil
30	97	16	severe restriction	not done	nil	nodularity

KEY TO MASTER CHART

Presenting sym	no sym	=	0
	Cough	=	1
	Dyspnea	=	2
	Hemoptysis	=	3
	Chestpain	=	4
Gen symptoms	no sym	=	0
	Fatigue	=	1
	Wt loss	=	2
	Fever	=	3
Pulm signs	tachypnea	=	1
	Crackles	=	2
	Rhonchi	=	3
	Cyanosis	=	4
	Clubbing	=	5
	Others	=	6
Lobe involved	RUL	=	1
	RML	=	2
	RLL	=	3
	LUL	=	4
	LLG	=	5
	LLL	=	6